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The Unfinished Business of U.S. Drug Safety Regulation

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I. INTRODUCTION

New safety risks often emerge after drugs have been approved and are in wide clinical use.¹ This situation was highlighted recently by the unanticipated cardiovascular risks of Cox-2 drugs,² the risk of suicide for children and adolescents taking antidepressants,³ the risks of rhabdomyolysis and kidney failure with cholesterol-lowering drugs,⁴ and risks for women taking hormone replacement therapy.⁵ A number of changes to the system for controlling drug safety in the United States either have been implemented or currently are being discussed. These include the recent creation of an independent Drug Safety Oversight Board within the U.S. Food and Drug Administration (FDA);⁶ proposals to enhance FDA's existing postmarket activities;⁷ collaborative risk-management approaches involv-

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¹ Alastair J.J. Wood, C. Michael Stein & Raymond Woosley, *Making Medicines Safer—The Need for an Independent Drug Safety Board*, 339 N. ENG. J. MED. 1851 (1998).

² Center for Drug Evaluation and Research (CDER), Food and Drug Admin. (FDA), Transcripts of Joint Meeting of the Arthritis Advisory Comm. and the Drug Safety and Risk Management Advisory Comm. (Feb. 16-18, 2005), *available at* <http://www.fda.gov/ohrms/dockets/ac/cder05.html> [hereinafter FDA, Joint Meeting Transcripts].

³ CDER, FDA, Labeling Change Request Letter for Antidepressant Medications (as updated Oct. 28, 2004), *available at* <http://www.fda.gov/cder/drug/antidepressants/SSRIlabelChange.htm>.

⁴ FDA, Detailed View: Safety Labeling Changes Approved by FDA Center for Drug Evaluation and Research (Sept. 2003), <http://www.fda.gov/medwatch/SAFETY/2003/sep03.htm>; CDER, FDA, FDA Public Health Advisory on Crestor (rosuvastatin) (Mar. 2, 2005), *available at* http://www.fda.gov/cder/drug/advisory/crestor_3_2005.htm.

⁵ FDA, FDA News: FDA Updates Hormone Therapy Information for Post Menopausal Women (Feb. 10, 2004), <http://www.fda.gov/bbs/topics/NEWS/2004/NEW01022.html>.

⁶ FDA, FDA Fact Sheet: FDA Improvements in Drug Safety Monitoring (Feb. 15, 2005), <http://www.fda.gov/oc/factsheets/drugsafety.html>.

⁷ *FDA's Drug Approval Process: Up to the Challenge?*, Hearing Before the S. Comm. on Health, Education, Labor & Pensions, 109th Cong., 1st Sess. (Mar. 1, 2005) (statement of Dr. Thomas Fleming, Professor & Chairman, Dep't of Biostatistics, Univ. of Washington), *available at* http://help.senate.gov/Hearings/2005_03_01/fleming.pdf; *id.* statement of William B. Schultz, Partner, Zuckerman Spaeder LLP, *available at* http://help.senate.gov/Hearings/2005_03_01/schultz.pdf; *Ensuring Drug Safety: Where Do We Go From Here?*, Hearing Before the S. Comm. on Health, Education, Labor & Pensions, 109th Cong., 1st Sess. (Mar. 3, 2005) (statement of Dr. Bruce Psaty, Univ. of Washington), *available at* http://help.senate.gov/Hearings/2005_03_03/psaty.pdf [hereinafter *Hearing on Drug Safety*].

ing FDA, the pharmaceutical industry, and physicians;⁸ and other proposed drug safety oversight activities either within, or independent of, FDA.⁹

This public dialogue has tended to focus on FDA and its activities, rather than looking beyond FDA at the broader legal framework for drug safety, which also may need reform and modernization. FDA plays a crucial role in drug safety, but the agency's powers are limited by the U.S. Constitution; by the Federal Food, Drug, and Cosmetic Act (FDCA);¹⁰ and by FDA's own regulations. Other players also are important. "Fixing" FDA may not fix the problem, therefore, without related changes to the overall framework in which the agency operates.

This article argues that the current drug safety framework lacks tools that are essential for selective risk management. Here, "selective" refers to an approach that seeks to manage and minimize risk, while still preserving the therapeutic benefits that risky products may offer to patients. This implies controlling drug-related injuries, whenever possible, by means other than simply keeping products off the market. An example of this approach would be to improve the targeting of therapies by screening patients to determine the right drug and dose for each individual and to identify patients with a heightened susceptibility to injury. Targeting requires a level of scientific understanding that still is unavailable for many drugs, although this science is developing rapidly. Another option would be to improve clinical drug safety compliance (i.e., making sure that known safety information is communicated effectively and put into practice). Still another option would be rapid detection and response when adverse reactions do occur, in order to lessen the resulting injuries.

Implementing a system of selective risk management would require scientific and technical work, and it also would require fundamental legal reforms. Addressing the technical issues is partly a question of resources. Developing data, techniques, and active surveillance systems to monitor and manage drug-related risks is costly. Promising efforts, such as those by the Agency for Healthcare Research and Quality (AHRQ) and Centers for Education and Research in Therapeutics (CERTs), have suffered under funding constraints.¹¹ Assuming the technical challenges can be overcome, there are fundamental problems with the way current U.S. laws and regulations approach risk management.

This was clear in February 2005 when an FDA advisory panel reviewed safety concerns with three popular Cox-2 painkillers, but ultimately voted to allow all three drugs to continue being sold.¹² What was troubling about this situation was that it displayed how few options FDA has available for managing drug safety problems. The advisory panel was faced with a stark, binary choice with potential casualties on either side. Patients who had come to rely on these drugs would suffer if they ceased to be avail-

⁸ *Hearing on Drug Safety*, *supra* note 7, statement of Dr. Cecil B. Wilson, American Medical Ass'n Board of Trustees, available at http://help.senate.gov/testimony/t208_tes.html; see also FDA, TASK FORCE ON RISK MANAGEMENT, MANAGING THE RISKS FROM MEDICAL PRODUCT USE (1999), available at <http://www.fda.gov/oc/tfrm/Tableofcontents.htm>.

⁹ Wood et al., *supra* note 1; Psaty Statement, *supra* note 7; see also *Hearing on Drug Safety*, *supra* note 7, statement of Dr. Raymond Woosley, Critical Path Inst., Univ. of Arizona, available at http://help.senate.gov/Hearings/2005_03_03/woosley.pdf.

¹⁰ Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040 (1938), as amended (codified at 21 U.S.C. §§ 301-399).

¹¹ See, e.g., AHRQ, Budget Limitation on AHRQ Large Research and Conference Grant Applications (Notice NOT-HS-04-007) (Aug. 5, 2004), <http://grants.nih.gov/grants/guide/notice-files/NOT-HS-04-007.html>; AHRQ, Special Emphasis Notice: Research Priorities for the Agency for Healthcare Research and Quality (Notice NOT-HS-05-005) (Nov. 30, 2004), <http://grants.nih.gov/grants/guide/notice-files/NOT-HS-05-005.html>.

¹² FDA, Joint Meeting Transcripts, *supra* note 2.

able,¹³ but continued sales of the drugs would harm patients who are susceptible to drug-related injuries. In these situations, FDA ultimately is reduced to flipping an “on/off” switch—to allow sale or not—and safety regulation is reactive. Regulators can react to the risk/benefit ratio, but they have little power to change the ratio by selectively reducing the risks.

This problem has historical origins. Many nations, including the United States, rely on drug regulations that were designed in the mid-twentieth century. Premarket review of drug safety in the United States dates back to passage of the FDCA in 1938, which was amended in 1951 to distinguish between prescription and over-the-counter drugs,¹⁴ and again in 1962 to require premarket review of drug efficacy, as well as safety.¹⁵ In that era, there was little understanding of why some people respond well to a drug while others respond adversely or not at all. Drugs, therefore, fell into the legal category of “unavoidably unsafe” products—products that provide benefits, but which, in the present state of human knowledge, cannot be made perfectly safe in their intended uses.¹⁶ Science and information technology did not support targeting of therapies or large-scale, real-time monitoring and analysis of clinical data. This limited the opportunities for selective risk management and the concept remained poorly developed in drug safety regulations. Preventing the sale of a drug became the primary regulatory tool for managing its risks—a strategy that avoids risk by sacrificing the drug’s benefits.

Despite incremental modernization in recent years, today’s drug safety regulations bear a lasting imprint of these earlier constraints. Until fundamental modernization takes place, FDA and its advisory committees will face harsh, unpleasant choices and the public will be denied the full measure of safety and therapeutic benefit that current technologies could support. By analogy, there are two ways to design a regulatory framework to prevent fire-related injuries. The first is to empower a regulator to approve, or disapprove, the sale of matches and other products that can start fires. The second is to allow these products to be sold, but implement forceful systems to manage their risks. These systems could include, for example, promoting research into fire-retardant technologies, establishing fire departments to respond promptly when fires do occur, and implementing programs to make sure that available safety warnings are understood and observed. The current drug safety regulatory framework remains heavily invested in the first strategy and underinvested in the second one, which exemplifies selective risk management.

II. BARRIERS TO SELECTIVE RISK MANAGEMENT

The United States will continue to face ongoing problems with drug safety until the government addresses three items of business that still are unfinished, almost seventy years after passage of the FDCA: 1) ensuring compliance with important safety warnings while preserving needed flexibility for physicians to adapt drug use to the individual patient; 2) developing a clearer distinction between pre- and postapproval safety regulation; and 3) devising mechanisms to promote adequate investment in safety improvements.

¹³ John Leland, *Pain Pills Withdrawn, Many Renew Search for Relief*, N.Y. TIMES, Mar. 6, 2005.

¹⁴ Durham-Humphrey Act, Pub. L. No. 82-215, 65 Stat. 648 (1951).

¹⁵ Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962).

¹⁶ RESTATEMENT (SECOND) OF TORTS § 402A, cmt. k (1977); Diane Schmauder Kane, *Annotation: Construction and Application of the Learned Intermediary Doctrine*, 57 A.L.R. 5th 1, § 2[a] (1998, updated through 2004); Sheryl Calabro, *Breaking the Shield of the Learned Intermediary Doctrine: Placing the Blame Where It Belongs*, 25 CARDOZO L. REV. 2241, 2250 (2004).

A. Promoting Compliance With Safety Warnings

Safe clinical use of drugs requires not only that standards of safe use be identified, but also that they be heeded and put into practice. A large-scale study found that labeling revisions and efforts to communicate contraindications of the drug cisapride (Propulsid™) had little real impact on prescribing behavior.¹⁷ Manufacturers ultimately removed cisapride, terfenadine (Seldane™), and astemizole (Hismanal™) from the market because of noncompliance with warnings, stated in each drug's labeling, that prescribing the drug in combination with certain other drugs (e.g., erythromycin) could cause life-threatening arrhythmias.¹⁸ Troglitazone (Rezulin™), bromfenac (Duracet™), and trovafloxacin (Trovan™) were removed from the open market due to noncompliance with labeling provisions aimed at managing liver toxicity, although the drugs, if used as directed in the labeling, were considered safe.¹⁹ Numerous studies have found patients suffer injuries because drugs are prescribed, dosed, taken, or monitored inappropriately, often in direct contravention of safety warnings contained in their labeling.²⁰

If failure to heed a drug's labeling results in injuries, FDA's principal recourse is to remove the drug from the market, either by withdrawing approval or, more commonly, through pressures that induce voluntary removal of the drug by the manufacturer.²¹ As discussed *infra*, FDA does not have the power to require that a drug stay on the market so that its benefits are preserved, but to enforce compliance with the drug's labeling provisions. FDA's accelerated approval program²² envisions nuanced safety management through special restrictions on use²³ but, again, provides no direct enforcement of the use restrictions—only withdrawal of the drug in the event of noncompliance.²⁴ This

¹⁷ W. Smalley, D. Shatin, D.K. Wysowski, J. Gurwitz, S.E. Andrade, M. Goodman, K.A. Chan, R. Platt, S.D. Schech & W.A. Ray, *Contraindicated Use of Cisapride: Impact of Food and Drug Administration Regulatory Action*, 284 JAMA 3036 (2000).

¹⁸ Raymond L. Woosley & Glenn Rice, *A New System for Moving Drugs to the Market*, ISSUES SCI. & TECH. ONLINE (Winter 2005), <http://www.issues.org/issues/21.2/woosley.html>.

¹⁹ *Id.*

²⁰ See, e.g., N. Barber, M. Rawlins & B. Dean Franklin, *Reducing Prescribing Error: Competence, Control, and Culture*, 12 QUALITY & SAFETY HEALTH CARE 29 (2003); Jerry H. Gurwitz & Paula Rochon, *Improving the Quality of Medication Use in Elderly Patients: A Not-So-Simple Prescription*, 162 ARCH. INTERN. MED. 1670 (2002); Timothy S. Lesar, *Tenfold Medication Dose Prescribing Errors*, 36 ANNALS PHARMACOTHERAPY 1833 (2002); Anne Bobb, Kristine Gleason, Marla Husch, Joe Feinglass, Paul R. Yarnold & Gary A. Noskin, *The Epidemiology of Prescribing Errors: The Potential Impact of Computerized Prescriber Order Entry*, 164 ARCH. INTERN. MED. 785 (2004); Eran Kozier, Dennis Scolnik, Alison Macpherson, Tara Keays, Kevin Shi, Tracy Luk & Koren Gideon, *Variables Associated With Medication Errors in Pediatric Emergency Medicine*, 110 PEDIATRICS 737 (2002); Lars Noah, *The Coming Pharmacogenomics Revolution: Tailoring Drugs to Fit Patients' Genetic Profiles*, 43 JURIMETRICS J. 1 (2002); see also INST. OF MED., COMM. ON QUALITY OF HEALTH CARE IN AMERICA, *TO ERR IS HUMAN: BUILDING A SAFER HEALTH SYSTEM* 27-43 (Linda T. Kohn, Janet M. Corrigan & Molla S. Donaldson eds., 2000) (discussing medication errors generally, including noncompliance with warnings and other types such as errors due to equipment failure or inaccurate diagnosis) [hereinafter IOM, *TO ERR IS HUMAN*].

²¹ Geoffrey M. Levitt, James N. Czaban & Andrea S. Patterson, *Human Drug Regulation*, in 2 FUNDAMENTALS OF LAW AND REGULATION: AN IN-DEPTH LOOK AT THERAPEUTIC PRODUCTS 178 (David G. Adams, Richard M. Cooper & Jonathan S. Kahan eds., 1999); see also I. Scott Bass, *Enforcement Powers of the Food and Drug Administration: Drugs and Devices*, *id.* at 70-74.

²² U.S. Dep't of Health & Human Servs. (HHS), FDA, New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval (Final Rule amending 21 C.F.R. Parts 314 and 601), 57 Fed. Reg. 58,942 (Dec. 11, 1992).

²³ HHS, FDA, New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval (Proposed Rule amending 21 C.F.R. Parts 314 and 601), 57 Fed. Reg. 13,234, 13,237 (Apr. 15, 1992).

²⁴ 21 C.F.R. § 314.530.

is not to say that FDA necessarily *should* have the power to enforce physician compliance with the safety information provided in a drug's labeling, but merely to point out that, without this power, it is difficult for FDA to manage a drug's risks while still preserving its benefits.

Selective risk management still would be possible, even in this situation, if there were a workable compliance framework outside FDA (e.g., through state regulation, the tort system, or voluntary efforts of the medical profession and healthcare industry). It then would be possible for FDA to continue to allow sale of the drug, while relying on external mechanisms to ensure compliance with important safety warnings related to the drug's use. As discussed *infra*, there is not, at present, a dependable compliance framework that FDA can rely on for this purpose. The absence of such a framework hinders selective risk management, sometimes to the point that a beneficial therapy is lost even though the drug could be safe if used in accordance with its labeling.

The fact that FDA cannot enforce physician compliance with a drug's labeling reflects a conscious division of authority under the FDCA for functions that might be described as standard setting and clinical compliance. FDA is involved in setting safety standards but does not enforce day-to-day physician compliance with them.

1. *Standard Setting*

There is not a formal, comprehensive list of "FDA safety standards" for each drug that FDA approves. Rather, standards are expressed indirectly through the drug's labeling and through other conditions FDA establishes for the manufacture, distribution, sale, and use of the drug. FDA-approved labeling provides instructions for safe use and discloses known risks, contraindications, and warnings.²⁵ Under FDA's accelerated approval program, the agency can impose special restrictions on distribution and use to address safety concerns.²⁶ As new risks arise, FDA can work with manufacturers to revise drug labeling, can require boxed warnings or warning letters to physicians, and can issue warnings to the public.²⁷ Collectively, these actions establish a *de facto* set of safety standards—a body of information, instructions, warnings, and conditions that FDA, based on the scientific evidence available to the agency, has deemed to be important for the safe use of a particular drug.

2. *Clinical Compliance*

Clinical compliance involves efforts to foster adherence to known safety standards and to deter high-risk prescribing practices. Direct federal or state regulatory enforcement is one option, but it has long been regarded warily. There are sound reasons to preserve significant discretion for physicians to weigh a drug's risks and benefits on a patient-by-patient basis and to prescribe drugs in ways not always consistent with their labeling. Labeling provisions are based largely on data from clinical trials, which do not necessarily capture the full range of health conditions and patient characteristics that physicians face in day-to-day practice.²⁸ Lack of data proving that a particular use is

²⁵ 21 C.F.R. § 201.55-.57; *see generally* 21 C.F.R. pt. 201, subpt. A (General Labeling Provisions) and subpt. B (Labeling Requirements for Prescription Drugs and/or Insulin).

²⁶ *Id.* § 314.520.

²⁷ *Id.* § 201.57(e); *see also* FDA, The FDA Safety Information and Adverse Event Reporting Program, Medical Product Safety Information, <http://www.fda.gov/medwatch/safety.htm> (last visited Feb. 6, 2005).

²⁸ Woosley & Rice, *supra* note 18.

safe does not amount to proof that the use is unsafe. Off-label use of drugs (i.e., prescribing drugs for medical indications, to patient subgroups, or in ways that clinical trials and labeling did not envision) often does produce a therapeutic benefit, which could be lost if there were rigid enforcement of drug labeling.

Alternative compliance mechanisms include, for example, drug-injury lawsuits, to the extent these lawsuits have a deterrent effect on high-risk prescribing practices; voluntary compliance efforts within the medical profession and healthcare and pharmaceutical industries; and technical "fixes," such as automated prescription order-entry systems that remind physicians of warnings at the time the prescriptions are written. A compliance mechanism not now in general use would be to require patients' informed consent for uses of drugs that directly contravene important safety provisions in the labeling of those drugs. This would promote physicians' awareness of the warnings that they are recommending be ignored, and it could reduce high-risk prescribing by giving patients an opportunity to opt out of the treatment.

Improving clinical drug safety requires, first, a clear understanding of where the problems lie. Are there problems with standard-setting, clinical compliance, or both? Because FDA is not heavily involved in clinical compliance, reforms that focus strictly on the agency may leave compliance issues unresolved. For example, one of the reforms proposed after the recent Cox-2 safety problems was to grant FDA greater power to require postapproval labeling revisions.²⁹ It is not clear, however, that additional tweaking of labeling can make drugs safe, when the safety standards reflected in drug labeling are widely disregarded.³⁰ Selective risk management involves both standard setting and compliance and, thus, may require reforms on both fronts.

Under the FDCA, responsibility for clinical compliance was left mainly to the states. There was a spirited legislative debate in the late 1930s, before passage of the FDCA, concerning the proper scope of state and federal power in this sensitive area of health policy.³¹ States traditionally had regulated the practice of medicine and offered redress, through lawsuits, for medical malpractice and product-related injuries. Congress made clear that by passing the FDCA, it did not intend to authorize broad FDA regulation of the practice of medicine.³² Courts have not found constitutional limits on FDA's power to regulate physicians,³³ but the agency, as a matter of policy, has sought to avoid direct regulation of their activities.³⁴ FDA has stated "labeling is not intended either to preclude the physician from using his best judgment in the interest of his patient, or to impose liability if he does not follow the package insert."³⁵ FDA decides whether a drug can be sold and approves its labeling, but does not enforce the safety standards reflected in the approved labeling.

²⁹ CNN, *FDA Wants to Dictate Warning Labels* (Mar. 1, 2005) (copy on file with authors); Aaron Levin, *FDA Officials Divided Over Need for Policy Change*, 40(7) *PSYCHIATRIC NEWS* 1 (2005); Press Release, Office of Senator Chris Dodd, Grassley, Dodd Expand Effort to Improve Drug Safety System (Apr. 27, 2005), available at <http://dodd.senate.gov/press/Releases/05/0427.htm>.

³⁰ Smalley et al., *supra* note 17; Amy Barrett, *Tough Warning Labels, Weak Results*, *BUS. WK.*, Apr. 13, 2005, available at www.msnbc.msn.com/id/7488711/.

³¹ Joel E. Hoffman, *Administrative Procedures of the Food and Drug Administration*, in 2 *FUNDAMENTALS OF LAW AND REGULATION*, *supra* note 21, at 17-24.

³² Dep't of Health, Education, and Welfare (HEW), FDA, *Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration* (Notice of Proposed Rulemaking), 37 Fed. Reg. 16,503-05 (July 30, 1972).

³³ David G. Adams, *The Food and Drug Administration's Regulation of Health Care Professionals*, in 2 *FUNDAMENTALS OF LAW AND REGULATION*, *supra* note 21, at 423.

³⁴ *Id.* at 425-26; see also 37 Fed. Reg. at 16,503-04.

³⁵ 37 Fed. Reg. at 16,504; William L. Christopher, *Off-label Drug Prescription: Filling the Regulatory Vacuum*, 48 *FOOD & DRUG L.J.* 247 n.6 (1993).

After passage of the FDCA, states could develop individual approaches for promoting physician compliance with the safety standards that flow out of FDA's regulatory process. Direct state regulatory enforcement was one possibility; it would have meant empowering state regulatory agencies to oversee physician compliance with drug labeling. As matters evolved after 1938, however, the states did not embrace this approach. Many state medical boards do monitor prescribing practices, but usually this is aimed at specific problems, such as over-prescribing of narcotic painkillers and other controlled substances, rather than at policing compliance with safety provisions in drug labeling.³⁶

Instead, lawsuits in state courts became an important *de facto* compliance mechanism at the state level.³⁷ The tort system serves several purposes, including compensation of injured parties, deterrence of behaviors that contribute to injuries, and corrective justice.³⁸ The deterrence aspect of tort litigation is what makes it a compliance mechanism: The threat of financial liability for drug-related injuries creates incentives for manufacturers to make their products safe and to provide accurate warnings, and it encourages physicians to heed known safety information.

When the FDCA was passed in 1938, it may have seemed plausible that the state tort system could provide an effective, albeit indirect, compliance mechanism. Privity-of-contract requirements traditionally had prevented consumers from suing product manufacturers with whom they had not dealt directly, as typically is the case with drug manufacturers. Such suits were becoming more common, however, by the 1930s.³⁹ Facing a real threat of such suits, drug manufacturers, it seemed, would have strong incentives to see that their products were prescribed in a safe manner.⁴⁰

A 1948 New York court decision⁴¹ weakened these incentives for manufacturers. Its approach later came to be known as the learned intermediary doctrine,⁴² and some form of this doctrine eventually was adopted by all fifty states.⁴³ The doctrine transfers key duties related to clinical drug safety from manufacturers to physicians, on the premise that the physician's prescribing decision ultimately controls the risks to which a patient is exposed.⁴⁴ In many states, listing a risk in the drug's labeling is sufficient to shift liability to the physician, even if the physician never actually read the warning.⁴⁵ Manufacturers still can be sued for risks that they failed to disclose in drug labeling, such as the recently discovered cardiovascular risks with Cox-2 drugs, but the learned intermediary doctrine tends to shield manufacturers from liability for disclosed risks. This encourages manufacturers to pack labeling with long and often indigestible lists of even small safety problems. It may not encourage them, however, to make sure the safety

³⁶ Diane E. Hoffmann & Anita J. Tarzian, *Achieving the Right Balance in Oversight of Physician Opioid Prescribing for Pain: The Role of State Medical Boards*, 31 J.L. MED. & ETHICS 21 (2003).

³⁷ Troyen A. Brennan & Marilyn Rosenthal, *Medical Malpractice Reform: The Current Proposals*, 10 J. GEN. INTERN. MED. 212 (1995).

³⁸ See GUIDO CALBRESI, *THE COSTS OF ACCIDENTS: A LEGAL AND ECONOMIC ANALYSIS* 24-33 (1970); DON N. DEWEES, DAVID DUFF & MICHAEL TREBILCOCK, *EXPLORING THE DOMAIN OF ACCIDENT LAW: TAKING THE FACTS SERIOUSLY* 5-9 (1996).

³⁹ *MacPherson v. Buick Motor Co.*, 217 N.Y. 382, 111 N.E. 1050 (1916); *see also* *Mason v. Am. Emery Steel Works*, 241 F.2d 906 (1957), *citing* 49 HARV. L. REV. 1050 (1936).

⁴⁰ Guido Calabresi & A. Douglas Melamed, *Property Rules, Liability Rules, and Inalienability: One View of the Cathedral*, 85 HARV. L. REV. 1089 (1972) (discussing incentives created by tort litigation); Andrew Barrett, *The Past and Future of Comment k: Section (4)(B)(4) of the Tentative Draft Restatement (Third) of Torts—Is It the Beginning of a New Era for Prescription Drugs?*, 45 SYRACUSE L. REV. 1291, 1298-303 (1995).

⁴¹ *Marcus v. Specific Pharm.*, 77 N.Y.S.2d 508 (N.Y. App. Div. 1948).

⁴² *Sterling Drug v. Cornish*, 370 F.2d 82, 85 (8th Cir. 1966).

⁴³ Calabro, *supra* note 16, at 2248.

⁴⁴ Kane, *supra* note 16, §§ 1[a], 2[a].

⁴⁵ *Id.* §§ 21-23.

warnings are effectively communicated and put into practice, because the mere presence of the warning tends to shift liability to physicians.

The shift of liability would seem to provide strong incentives for physicians to heed safety warnings. In practice, however, lawsuits have not functioned ideally as a clinical compliance mechanism. One reason is that courts apply medical malpractice rules, rather than product liability law, when physicians are sued for drug-related injuries.⁴⁶ Malpractice rules measure a physician's duty relative to a professional standard⁴⁷ (What do other physicians do?) rather than to an objective standard (What really is reasonable, in light of the facts?) or a regulatory standard (What does FDA deem safe?). Ignoring safety warnings may carry no negative financial consequence for the physician, if disregard is so widespread as to become the professional standard. This weakens the deterrent effect of tort litigation. Some states do treat labeling and package inserts as the standard of care, but many states treat it as just one factor to consider.⁴⁸

Another problem is that malpractice suits do not provide a clear, consistent link between prescribing practices and financial consequences. Empirical studies have found that fewer than two percent of negligent medical injuries actually result in a malpractice claim.⁴⁹ Conversely, a study of 3,500 malpractice claims found that only seventeen percent actually involved a negligent injury.⁵⁰ Unsafe prescribing practices may go unpunished even as prudent ones draw large penalties. The tort system provides a "fragmented and capricious response" to injuries.⁵¹ Effective deterrence requires precision: those claims—and only those claims—that involve a negligent injury should be compensated.⁵² Lacking this precision, drug-injury lawsuits are not a strong compliance mechanism.⁵³

The United States has an incomplete legal framework for drug safety. This may come as a surprise, given how often it is characterized as comprehensive or even overbearing. The government and industry expend great effort to develop drug safety standards, but the system lacks dependable means to promote day-to-day compliance with the standards. FDA does not directly enforce safe prescribing practices; there is little direct regulatory enforcement at the state level; state tort lawsuits, at best, provide a spotty set of incentives for compliance; and much depends on voluntary efforts. Taken as a whole, the current legal framework is not toothless, but it only has one big tooth: to

⁴⁶ Linda A. Sharp, *Annotation: Malpractice: Physician's Liability for Injury or Death Resulting From Side Effects of Drugs Intentionally Administered to or Prescribed for a Patient*, 57 A.L.R. 5th 433, § 2[a] (1997, updated through 2004).

⁴⁷ WILLIAM J. CURRAN, MARK A. HALL, MARY ANNE BOBINSKI & DAVID ORENTLICHER, *HEALTH CARE LAW AND ETHICS* 314-37 (5th ed. 1998).

⁴⁸ Sharp, *supra* note 46, §§ 2[a], 7; David Carl Minneman, *Annotation: Medical Malpractice: Drug Manufacturer's Package Insert Recommendations as Evidence of Standard of Care*, 82 A.L.R. 4th 166, §§ 2-6 (1990, updated through 2004).

⁴⁹ Brennan & Rosenthal, *supra* note 37, at 213; Troyen A. Brennan, Lucian L. Leape, Nan M. Laird, Liesi Hebert, A. Russell Localio, Ann G. Lawthers, Joseph P. Newhouse, Paul C. Weiler & Howard H. Hiatt, *Incidence of Adverse Events and Negligence in Hospitalized Patients: Results of the Harvard Medical Practice Study I*, 324 N. ENG. J. MED. 370-76 (1991) (examining medical injuries generally, rather than drug-related injuries specifically).

⁵⁰ A. Russell Localio, Ann G. Lawthers, Troyen A. Brennan, Nan M. Laird, Liesi E. Hebert, Lynn M. Peterson, Joseph P. Newhouse, Paul C. Weiler & Howard H. Hiatt, *Relation Between Malpractice Claims and Adverse Events Due to Negligence: Results of the Harvard Medical Practice Study III*, 325 N. ENG. J. MED. 245-51 (1991).

⁵¹ Albert C. Lin, *Beyond Tort: Compensating Victims of Environmental Toxic Injury*, 78 S. CAL. L. REV. 1439, 1500 (2005) (discussing conclusions of NEW ZEALAND COMM'N OF COMP. FOR PERSONAL INJURY, COMPENSATION FOR PERSONAL INJURY IN NEW ZEALAND: REPORT OF THE ROYAL COMMISSION OF INQUIRY (1967)).

⁵² Brennan & Rosenthal, *supra* note 37, at 212.

⁵³ *Id.*; see also Brennan & Leape et al., *supra* note 49, at 372.

remove products from the market (or to threaten to do so). As a result, postapproval drug safety regulation is binary and reactive, and risks often can be managed only at the cost of benefits.

B. Distinguishing Pre- and Postapproval Standard Setting

Selective risk management also calls for modernization of the regulatory standard-setting process. In particular, it requires a clearer distinction between pre- and postapproval drug safety regulation and the safety standards needed at each phase. Current FDA regulations impose various new inspection, monitoring, and reporting requirements⁵⁴—some only voluntary⁵⁵—that come into effect after a drug is approved. However, there is little real change in FDA's decisional power, in the scope of its jurisdiction, or in the concept of drug safety itself, following drug approval. FDA's postapproval decision authority, in many respects, is limited to affirming or reversing its own prior decisions, using the same types of data and methodologies that then were relevant. An earlier-granted approval can be withdrawn, for example.

Rethinking past decisions may not be the best way to manage uncertainties inherent in the future. *Factors that bear on what is safe, for purposes of justifying an initial drug approval, are not necessarily the same factors that determine whether a drug will be safe in actual clinical use.* FDA's postmarket monitoring and reporting emphasize collection of data that would have been relevant during premarket approval (e.g., adverse events related to drug use),⁵⁶ rather than creation of new information specifically relevant to safe clinical use (e.g., data explaining why some people react badly, data identifying ways to spot those people before drugs are administered, and data identifying the best procedures to detect and mitigate the harms that do occur).

Risks known at the time of approval must be disclosed in labeling,⁵⁷ but are tolerated in the following sense: If an approved drug produces adverse events that were identified during pre-approval clinical trials, and which occur at roughly the same frequency that the trials predicted, the manufacturer generally is not required to take steps to reduce the rate at which those adverse events occur. Much of the effort of postapproval regulation instead is dedicated to detecting and reporting *new* risks as they are discovered. Thus, FDA calls for immediate reporting, in fifteen days, of new risks, (i.e., adverse drug experiences that are both serious and unexpected).⁵⁸ Other adverse experiences, including expected ones, are reported periodically,⁵⁹ but these data are not used in a systematic goal-setting process to reduce their frequency. Moreover, it is estimated that data reported to FDA cover only one to ten percent of all adverse events that actually occur, and between one third and one half of all the serious adverse events.⁶⁰ *Current regulations tolerate a level of "unavoidable" risk that may be increasingly avoidable in the future, as the science of selective risk management improves.*

This, again, reflects historical factors. Mid-twentieth century information technology could not support large-scale, continuous, real-time monitoring of data from actual

⁵⁴ 21 C.F.R. § 314.80-.81.

⁵⁵ Wood et al., *supra* note 1.

⁵⁶ 21 C.F.R. § 314.80.

⁵⁷ Kane, *supra* note 16, § 2[a].

⁵⁸ 21 C.F.R. § 314.80(a), (c)(1)(i)-(ii).

⁵⁹ *Id.* § 314.80(c)(2).

⁶⁰ Public Broadcasting System, Transcript of Interview with Paul Seligman, Director of the Office of Pharmacoeconomics and Statistical Sciences and Director of the Office for Drug Safety, CDER, FDA (Nov. 4, 2002), *available at* <http://www.pbs.org/wgbh/pages/frontline/shows/prescription/interviews/seligman.html>.

clinical use of approved drugs. As a result, regulations did not conceive standard setting as an ongoing, real-time adaptive process that continuously incorporates lessons from today's clinical experience to refine the management of risks tomorrow. As technology has improved, so have opportunities for risk management. To take advantage of this, regulations would need to re-conceive what safety standards are.

In addition to FDA's existing standard-setting activities (e.g., review of drug labeling), there is a need for postapproval standards that specifically address the challenge of making drugs as safe as possible when and as they actually are prescribed. Postapproval safety standards might include, for example, standards for when and how patients should be screened to assess their susceptibility to drug-related injury; monitoring procedures to ensure prompt detection of certain types of serious drug reactions; recordkeeping procedures to ensure the monitoring takes place; and best treatment protocols to mitigate harms that are experienced by patients. Developing these standards would require new data that go beyond what FDA currently collects.

The task would require expanded access to outcomes data and other clinical information, as well as data from laboratory studies of biomarkers (e.g., data explaining individual variations in drug response). Developing and using these data to establish postapproval safety standards would require efforts both within and outside FDA. Some states already have efforts underway to develop statewide clinical information systems⁶¹ and electronic medical records to help identify, study, and prevent adverse drug reactions. State and federal coordination would be needed to ensure system interoperability and consistent privacy protections, and to resolve how to finance further work on these systems.

The funding of laboratory studies also presents challenges. Much of the research needed for selective risk management is basic science rather than product-specific research, and manufacturers may be unwilling to shoulder the cost of this additional research. For example, genetic research to support better targeting of one drug may produce information relevant to other drugs, creating a free-rider problem as manufacturers wait for others to take the lead. Federal funding agencies such as the National Institutes of Health (NIH) may need to provide leadership, both in setting priorities and in providing funding. NIH traditionally has played a major role in funding the basic *upstream* scientific research that precedes drug development. Selective risk management implies a corresponding need for basic *downstream* research—basic science to improve clinical safety after drugs are developed and approved. Funding for this research, at present, is severely limited.

As the necessary data become available, there is the question of how best to harness the data into useful postapproval safety standards. Along with FDA, AHRQ and CERTs could play important roles in an expanded standard-setting effort, if adequate funding mechanisms are put in place.

C. Funding the Costs of Improved Clinical Safety

One of the greatest challenges in improving drug safety is to promote investment in incremental safety efforts, such as postapproval drug safety studies, clinical data gathering and surveillance, safety education, and development of postapproval safety standards. A major defect of the current U.S. drug safety framework is the lack of workable financing mechanisms for these safety efforts. Resolving the financing problem may require statutory amendments and other broad legal reforms.

⁶¹ See, e.g., Massachusetts eHealth Collaborative, <http://www.maehc.org> (last visited Feb. 8, 2006).

The United States, as discussed *supra*, relies heavily on state tort lawsuits as a clinical compliance mechanism. By design, the tort system compensates prior victims; it is not a cost-sharing mechanism to gather funds for prospective investment in safety-related projects. This is a more serious failing today than it was in the mid-twentieth century, when the United States first came to rely heavily on lawsuits to address drug-related injuries. In coming years, pharmacogenomics and other risk-management technologies may offer real prospects to improving drug safety, but only if there is adequate investment in these technologies. Rather than simply compensating victims for “unavoidable” injuries, today’s compliance system needs to gather funds to invest in projects that gradually will make drug-related injuries more avoidable; lawsuits, by design, do not serve this latter objective. Printed labeling, for example, is a 1938 technology, and studies suggest that drug safety could be improved through computerized prescription order-entry systems that alert physicians to warnings and contraindications at the time prescriptions are written.⁶² Lawsuits cannot finance an improvement of this type; they merely compensate the harms that result, if the improvement is not made.

The FDCA and FDA’s regulations do not adequately address the funding problem. FDA has significant power to promote clinical drug safety through the regulation of drug manufacturers, even without directly regulating the physicians, providers, and pharmacists. In theory, drug manufacturers could serve as a fulcrum to promote drug safety compliance throughout the industry (e.g., FDA could enlist manufacturers to monitor how their drugs actually are being prescribed and to provide remedial training to address unsafe prescribing practices). In reality, however, there are problems with this approach. There are statutory limits on FDA’s power to order manufacturers to make safety improvements, but—even when that is not a problem—there are practical limits. Specifically, drug manufacturers have no legal duty to continue selling an approved drug that is known to help people, if doing so would be unprofitable. The pharmaceutical industry is not subject to the service obligations seen in many other regulated industries (e.g., public utilities), where suppliers, once they offer a service and induce public reliance on it, cannot stop offering it without regulatory approval to do so.⁶³ In those industries, suppliers cannot simply cease operations to avoid the cost of making consumers safe. Drug manufacturers, in contrast, have the option of withdrawing a drug as an alternative to incurring costs to address its safety problems.

There are sound policy reasons for *not* imposing general service obligations on drug manufacturers. Industries operating under these obligations usually are ones—such as electric power transmission—where price regulation provides regulated companies with a reasonable guarantee of cost recovery, which is not the case with pharmaceuticals. FDA traditionally has been sensitive to the fact that drug manufacturers operate in a competitive environment where the long-term availability of new drugs depends on sound industry economics. This and other concerns—such as whether a drug manufacturer could be exempted from product liability if it were selling a drug against its own preference—make service obligations problematic. When the accelerated approval program was debated in 1992, public comments sought a service obligation to protect patients who were benefiting from drugs that later had to be withdrawn due to side effects in other subpopulations. FDA rejected the suggestion.⁶⁴

⁶² Bobb et al., *supra* note 20; Barber et al., *supra* note 20; Craig F. Feied, Jonathan A. Handler, Mark S. Smith, Michael Gillam, Meera Kanhouwa, Todd Rothenhaus, Keith Conover & Tony Shannon, *Clinical Information Systems: Instant Ubiquitous Clinical Data for Error Reduction and Improved Clinical Outcomes*, 11(11) ACADEMIC EMERGENCY MED. 1162 (2004).

⁶³ J. GREGORY SIDAK & DANIEL F. SPULBER, DEREGULATORY TAKINGS AND THE REGULATORY CONTRACT: THE COMPETITIVE TRANSFORMATION OF NETWORK INDUSTRIES IN THE UNITED STATES 113-28 (1998).

⁶⁴ Accelerated Approval Final Rule, 57 Fed. Reg. at 58,949, § IV.C.15.

The lack of a service obligation hinders selective risk management, because drugs can be withdrawn to avoid the cost of managing their risks. The solution does not lie in imposing service obligations; rather, it lies in developing better mechanisms to finance postapproval safety measures. FDA lacks the power, under current statutes and regulations, to require parties other than the manufacturer to help bear the costs of improving drug safety. This situation arguably is unjust, because parties other than the manufacturer do share the benefits of drug safety improvements. Private health insurers and governmental payers may experience reduced claims for drug-related injuries; providers and physicians may enjoy reduced malpractice liability; and adverse-responding patients, if they could be identified in advance, might avoid harm by not purchasing the drug. With no way to elicit contributions from these other parties, there often is no practical way for FDA to fix safety problems while still preserving a pipeline of commercially available drugs.

Currently, FDA must proceed cautiously in the knowledge that imposing additional safety requirements, even in an earnest attempt to save a drug that benefits responding patients, may destroy the drug's profitability thus making it just as unavailable as a regulatory nonapproval would have done. This caution can be seen in FDA's approach to postmarket studies. Traditionally, FDA lacked a clear statutory mandate to require postmarket studies of drug products,⁶⁵ although the agency claimed that it could require such studies as part of FDA's general powers to enforce the FDCA and to require drug companies to provide data bearing on whether previously granted approvals should be withdrawn.⁶⁶ FDA did not apply this power aggressively and across-the-board, however, as a tool to develop new data for postapproval risk management.

The 1992 accelerated approval program clearly authorized FDA to require postmarket studies of effectiveness (to confirm the relation of surrogate endpoints to actual clinical benefits),⁶⁷ but not of safety. In response to industry concerns, FDA declined to require timely completion of the postmarket studies by a specific date, and recent data show that completion rates, in fact, have been poor.⁶⁸ FDA also offered assurances that postmarket studies would be required only in narrowly defined circumstances, usually involving completion of a test already underway at the time of approval and in no event going beyond what usually is required in premarket clinical trials.⁶⁹ Under a self-imposed limit not to go beyond premarket data gathering, how can FDA optimize the safe clinical use of drugs? As already discussed, pre- and postmarket safety regulations require entirely different types of data.

The problem, then, is not simply whether FDA has the actual authority to order safety improvements, but that the agency lacks a way to spread the costs fairly among all of the parties that stand to benefit from increased drug safety. FDA's statutory authority could be expanded to allow the agency to collect fees for clinical safety measures from parties other than the drug manufacturer, and then apply these funds to safety-related projects. This approach, however, would embroil FDA in contentious issues of economic regulation for which it has neither the staffing nor experience, given its traditional role as a scientific regulator. Moreover, a centralized regulatory financing mechanism of this sort would be complex to administer, given the sheer size of the U.S. pharmaceutical and healthcare industries.

⁶⁵ Schultz Statement, *supra* note 7.

⁶⁶ 21 U.S.C. §§ 371(a), 355(k) (FDCA §§ 701(a), 505(k)); *see also* Levitt et al., *supra* note 21, at 179.

⁶⁷ 21 C.F.R. § 314.510.

⁶⁸ Susan Okie, *What Ails the FDA?*, 352 N. ENG. J. MED. 1063 (2005).

⁶⁹ Accelerated Approval Proposed Rule, 57 Fed. Reg. at 13,236, § III.A.2; Accelerated Approval Final Rule, 57 Fed. Reg. at 58,942, § II.C and at 58,953-54, §§ IV.F.28-32.

In summary, the tort system, by its nature, does not gather funds to invest in future safety improvements. FDA presently does not have the authority to implement a broad cost-sharing mechanism for this purpose. Even if the agency did have the authority, a centralized regulatory cost-sharing framework raises practical concerns. The problem of funding postapproval safety measures has never been satisfactorily resolved. Selective risk management will require better financing and cost-sharing mechanisms than exist today.

III. DIRECTIONS FOR REFORM

A simple test of any reform proposal is how well it addresses the three challenges just identified: 1) promoting clinical compliance with known safety information while preserving the valid role of physicians' discretion; 2) developing an adaptive process to set standards for the safe use of approved drugs, based on lessons learned in actual clinical practice; and 3) promoting investment in clinical safety improvements. This section focuses on the first and third of these challenges and the legal reforms that may be needed to address them.

The second challenge—postapproval standard setting—in many respects is a scientific and technical challenge, which involves identifying the current best practices for using drugs safely in the clinic while actively managing their risks, and developing the necessary data and information systems to support this process. These databases and information systems present various legal issues (e.g., informed consent and privacy protection). Arguably, though, the greatest barrier to postapproval standard setting is not whether today's technology can support it, or whether the ancillary legal issues can be resolved, but how to pay for it. Thus, addressing the third challenge is key to the second. The two crucial *legal* reform challenges are to develop workable compliance and funding mechanisms.

Reforms that focus entirely on FDA—even if they envision a significant expansion of the agency's statutory authority—cannot fully address these challenges. Concerning clinical compliance, there are good reasons *not* to make FDA a direct federal enforcer of safe prescribing practices. This was true when the FDCA was being debated in the 1930s, and it remains true today. Promoting safe clinical use of drugs possibly is too complex a task to be done in a centralized, top-down way, especially by an agency that is as compactly staffed as FDA, relative to staffing levels at other major federal agencies. FDA would face ongoing jurisdictional clashes with state medical boards and could face objections from patient advocacy groups and others wishing to preserve discretion for physicians to recommend off-label uses—including uses that, in individual cases, may run counter to known safety warnings. Moreover, there are inherent conflicts of interest in having a single agency set and enforce safety standards. FDA is not the logical locus of reforms to improve clinical compliance and, as already noted, an FDA-administered financing mechanism may not offer a practical solution to the funding problem. These challenges call for broader reforms.

A. Reforming Elements of the Existing Safety Framework

The broader drug safety framework, of which FDA is one part, includes other federal and state agencies, courts, and nongovernmental activities. Reforms could enhance, for example, the role of state regulators, the role of drug-injury tort litigation, and the role of voluntary efforts to promote drug safety. This section examines prospects for addressing the compliance and funding challenges through these existing elements of the drug safety framework.

The original vision of the FDCA was that states would have primary responsibility for clinical compliance to the extent it is a medical practice issue. State regulators could increase their direct oversight of physician prescribing practices as a way to improve drug safety. This approach raises many of the same concerns already noted in connection with FDA enforcement. Direct regulatory enforcement, whether state or federal, may unduly limit physicians' discretion and sacrifice potential therapeutic benefits associated with off-label use of drugs. Moreover, clinical safety requires the combined efforts of many parties including, among others, physicians, other healthcare providers, manufacturers, insurers, and advertisers and their regulators.⁷⁰ States may lack jurisdiction to involve all of these parties. Additional compliance efforts at the state level may be part of the solution, but appear insufficient on their own.

With regard to the funding problem, a state regulator would face many of the same issues FDA would face in implementing a centralized regulatory cost-sharing mechanism, and jurisdictional issues may narrow the pool of parties from which a state could gather funds. This does not appear promising as a comprehensive solution. Moreover, state efforts to gather and apply funds would need to be coordinated at a national level in order to set overall priorities and to ensure common technical standards.

The opposite extreme from direct regulatory enforcement would be to rely primarily on voluntary compliance efforts. Voluntary efforts can play, and in some instances already are playing, an important role in improving drug safety, while avoiding the problem of unduly limiting physicians' discretion. Unfortunately, voluntary measures, to date, have not provided the dependable clinical compliance framework and levels of investment needed to support selective risk management.

Because lawsuits are an important *de facto* compliance mechanism, tort reform is another possible approach to improve clinical compliance. Such reforms would need to strengthen incentives both for physicians to follow safe prescribing practices and for manufacturers to promote safe use of their drugs. These tort reforms differ from the "conventional" malpractice reforms that many states have pursued since the 1980s,⁷¹ which generally focus on reducing the number of claims, eliminating frivolous suits, or placing caps on noneconomic damages.

One way to enhance physicians' incentives would be for state legislatures to adopt a standard of care that requires a physician to adhere to the safety provisions included in a drug's labeling, unless the physician documents why adherence is not in the patient's best interest. This approach still would allow physicians to exercise discretion, but would require them to exercise it deliberately. Alternatively, states could provide an informed-consent tort remedy for patients who were not informed that a safety warning was being ignored. This approach, too, would preserve discretion for physicians to disregard safety warnings, subject to informed consent. Another, and possibly more controversial, approach would be to enact federal legislation that preempts the existing hodge-podge of state liability standards and allocates responsibilities for clinical drug safety more clearly among manufacturers, providers, physicians, pharmacists, and other concerned parties.

Strengthening manufacturers' incentives may require adjustments to the learned intermediary doctrine, which shifts much of the responsibility for clinical drug safety from manufacturers to physicians. One possible approach is to require manufacturers to "earn" protection under the learned intermediary doctrine on a case-by-case basis, by showing that the individual company has taken steps to promote safe use of the drug that generated the lawsuit.⁷² Such steps might include, for example, basing sales repre-

⁷⁰ IOM, *To Err Is Human*, *supra* note 20, at 37.

⁷¹ Brennan & Rosenthal, *supra* note 37, at 213.

⁷² Calabro, *supra* note 16; Timothy S. Hall, *Reimagining the Learned Intermediary Rule for the New Pharmaceutical Marketplace*, 35 SETON HALL L. REV. 193 (2004).

sentatives' commissions on how well, rather than how often, drugs are prescribed—an approach that reportedly already is in use by one manufacturer.⁷³ Other steps could include postmarket studies, tracking of actual prescribing practices, and safety education efforts to ensure that physicians understand and heed important safety warnings.

Even if done well, tort reform leaves some basic issues unresolved. The threat of lawsuits provides only an indirect incentive for prospective safety improvements⁷⁴ and it can have the perverse effect of undercutting drug safety. The fear of lawsuits may reduce incentives for manufacturers to acquire better information about the risks of drug products already in use.⁷⁵ Manufacturers that make an extra effort to monitor clinical outcomes and conduct postmarket research to identify drug safety problems are not immune from then having the results of these efforts turned against them in court.⁷⁶ Paradoxically, the threat of lawsuits also may cause manufacturers to leave dangerous products on the market *longer* than they should, fearing that recall would be seen as an admission that the product harms patients and thus invite a flood of litigation.⁷⁷ Blame-based systems work against transparency and frank disclosure, which actually may be the keys to fixing safety problems.⁷⁸

If the United States continues to rely heavily on lawsuits as a mechanism to promote safe clinical use of drugs, it may not be possible to resolve today's drug safety problems. The tort system, as noted *supra*, produces only a spotty correspondence between actions and consequences, which is incompatible with selective risk management. Meeting the two key challenges—clinical compliance and funding of future safety investments—ultimately may require replacing, rather than reforming, the role of tort litigation in the overall U.S. framework for drug safety.

B. An Insurance-Based Alternative to Drug-Injury Lawsuits

An insurance-based framework for drug-injury compensation may offer advantages in meeting these challenges. There have been various proposals to adopt a no-fault system for managing medical risks;⁷⁹ this approach would supplant malpractice suits with an insurance-based system to compensate iatrogenic injuries.⁸⁰ The United States is unlikely ever to replace its medical malpractice system *in toto*. However, these concepts merit consideration for the subset of physician malpractice suits that involve drug-related injuries and for product liability suits against drug manufacturers.

An insurance-based system is not an untested concept. Pharmaceutical injury insurance pools have operated in Sweden since 1978⁸¹ and Finland since 1984,⁸² and an

⁷³ Woosley & Rice, *supra* note 18.

⁷⁴ Patricia M. Danzon, *Alternative Liability Regimes for Medical Injuries: Evidence From Simulation Analysis*, 61 J. RISK & INSURANCE 219 (1994); Patricia M. Danzon, *Alternative Liability Regimes for Medical Injuries*, 15(54) GENEVA PAPERS ON RISK & INS. 3 (1990); Michael J. Saks, *If There Be a Crisis, How Shall We Know It?*, 46 MD. L. REV. 63 (1986).

⁷⁵ Omri Ben-Shahar, *How Liability Distorts Incentives of Manufacturers to Recall Products* 21-23 (2005) (discussion paper, University of Michigan John M. Olin Center for Law & Economics); <http://www.law.umich.edu/centersandprograms/olin/papers.htm>.

⁷⁶ IOM, *To ERR IS HUMAN*, *supra* note 20, at 109-31 (discussing difficulties in protecting voluntary reporting systems from legal discovery).

⁷⁷ *Id.* at 18-19.

⁷⁸ Bryan A. Liang, *Promoting Patient Safety Through Reducing Medical Error: A Paradigm of Cooperation Between Patient, Physician, and Attorney*, 24 S. ILL. U. L.J. 541 (2000).

⁷⁹ *Id.*; see also Brennan & Rosenthal, *supra* note 37, at 216-18.

⁸⁰ Patricia M. Danzon, *The Swedish Patient Compensation System: Lessons for the United States*, 15 J. LEGAL MED. 199 (1994).

⁸¹ Läkemedelsförsäkringsföreningen, *The Pharmaceutical Insurance in Sweden: Pharmaceutical Insurance*, http://www.lakemedelsforsakringen.se/html/eng/english_insurance.php (last visited Feb. 8, 2006).

⁸² Pharma Industry Finland, *The Medicines-Related Injuries Insurance*, http://www.pif.fi/page.php?page_id=140 (last visited Feb. 8, 2006).

insurance framework has been proposed as a way to address blood-product injuries in Canada.⁸³ The United States implemented a no-fault National Vaccine Injury Compensation Program (NVIC) in the 1980s for certain categories of vaccine-related injuries.⁸⁴ In other areas, insurance-based frameworks have replaced tort claims to compensate pollution-related injuries in Japan and accident-related and medical injuries in New Zealand.⁸⁵ These programs are similar to workers' compensation schemes adopted by all fifty U.S. states in the 1910s and 1920s, insofar as injured persons give up the right to bring ordinary lawsuits in return for swifter, more consistent compensation through a special administrative claims process that is funded by payment of insurance premiums.⁸⁶ For NVIC, these funds are collected through a seventy-five cent excise tax on every dose of covered vaccine purchased.⁸⁷

There are various ways the drug-injury compensation framework could be structured. Two basic features are critical, however, if the framework is to be effective in promoting clinical compliance and safety-related investments.

1. *Definition of Covered Parties*

The covered parties need to be entities that can exert direct and meaningful control over drug-related risks. These parties would purchase coverage and pay premiums into the insurance system, in return for which they would be exempt from ordinary tort liability for drug-related injuries. There could be several categories of covered parties: drug manufacturers; physicians and other healthcare providers; hospitals; clinical laboratories that provide screening tests used in drug targeting; pharmacists and distributors; and even health insurers, to the extent their formulary decisions affect the availability of drugs that will be safe for given patient subpopulations. Naturally, the difficulty of designing an insurance framework increases, as more categories are included. There may be advantages to limiting the categories of coverage offered initially, and then expanding coverage to others at a later time.

At a minimum, the insurance framework would need to cover drug manufacturers and physicians. Without the participation of these two groups, crucial aspects of drug safety could not be addressed through the insurance framework, because the entities best able to control product safety, marketing, and prescribing practices would not be involved. While drug-injury suits against pharmacists, hospitals, and other players do occur, the major categories of drug-injury litigation are suits against manufacturers and physicians. If the insurance framework is to provide a meaningful alternative to the tort system, both physicians and manufacturers need to be covered from the outset.

⁸³ Canadian Hemophilia Society, Blood Injury Compensation Scheme (adopted by Board of Directors on Feb. 7, 1995; amended May 1996), <http://www.hemophilia.ca/en/1.2.4.php>.

⁸⁴ HHS, Health Resources and Services Administration (HRSA), Fact Sheet: National Vaccine Injury Compensation Program, www.hrsa.gov/osp/vicp/fact_sheet.htm (last visited Feb. 8, 2006); Jaclyn Shoshana Levine, *The National Vaccine Injury Compensation Program: Can It Still Protect an Essential Technology?*, 4 B.U. J. Sci. & Tech. L. 9 (1998).

⁸⁵ Lin, *supra* note 51, at 1493-504 (discussing Japan's pollution-injury and New Zealand's accident-related injury compensation frameworks); Brennan & Rosenthal, *supra* note 37, at 216 (discussing no-fault medical-injury compensation frameworks in Sweden, Finland, and New Zealand).

⁸⁶ Price V. Fishback & Shawn Everett Kantor, *The Adoption of Workers' Compensation in the United States 1900-1930* (Nov. 1996) (NBER Working Paper No. 5840), *reprinted in* 41 J.L. & Econ. 305 (1998); RACHEL KAGANOFF STERN, MARK A. PETERSON, ROBERT REVILLE & MARY E. VAIANA, FINDINGS AND RECOMMENDATIONS ON CALIFORNIA'S PERMANENT PARTIAL DISABILITY SYSTEM: EXECUTIVE SUMMARY 1 (Rand Report MR-919-ICJ, 1997); PRICE V. FISHBACK & SHAWN EVERETT KANTOR, A PRELUDE TO THE WELFARE STATE: THE ORIGINS OF WORKERS' COMPENSATION (2000).

⁸⁷ HHS, HRSA, How is the vaccine injury compensation program funded? (answer ID 353, created Apr. 7, 2005; updated Aug. 23, 2005), <http://answers.hrsa.gov/cgi-bin/hrsa.cfg/php/enduser/home.php>.

2. *Method of Determining Insurance Premiums*

It would reduce incentives to improve drug safety, if manufacturers whose products rarely produce any injuries were required to pay the same insurance premiums as manufacturers of higher-risk products, or if physicians who strive to comply with safety warnings were forced to pay the same premiums as physicians who follow high-risk prescribing practices. Similar incentive problems have caused concern with the Swedish no-fault medical-injury compensation system and with birth-related neurological injury compensation programs adopted in Virginia and Florida in the 1980s.⁸⁸

To create strong incentives for clinical compliance, the proposed drug-injury insurance system would need to reward safe products and safe prescribing practices with lower premiums. Rather than pooling risks broadly across covered parties, premiums should be experience-rated (i.e., based on prior safety performance as reflected in actual patterns of claims for injuries) and should take account of current factors that bear on future risks (e.g., evidence that investments are being made to resolve safety problems).

Covered parties would pay different premiums, depending on how risky each party's particular products and practices actually are—a judgment that would be based on various factors. In the case of manufacturers, these factors might include the risk profiles of the manufacturer's product offerings, compliance with FDA's good manufacturing practices, and programs the manufacturer has put in place to educate physicians on safe prescribing and patient-monitoring practices. Postmarket studies could be required as a condition for insuring drugs with suspected safety issues, or such studies could be encouraged by offering reductions in premiums upon completion of a study. In the case of physicians, premiums might be based on actual prescribing patterns, adherence to safety standards reflected in FDA-approved labeling, documented use of follow-up testing to detect and mitigate adverse drug reactions, and actual clinical outcomes.

Basing insurance premiums on experience and risk factors has the effect of integrating a process of postapproval standard setting into the insurance framework. This process identifies factors that affect clinical safety, harnesses clinical and other data to measure safety performance, and appraises the likely effectiveness of incremental safety measures. Insurance costs reflect each party's measured performance against a set of postapproval safety standards developed during the premium-setting process.

The insurance framework could be implemented state-by-state or through federal legislation that preempts state tort remedies for drug-related injuries and authorizes the creation of an insurance-based framework. Centralized administration could be problematic, given the size of the U.S. healthcare system. An insurance framework offers opportunities to achieve varying degrees of decentralization, depending on how the framework is designed. As with the workers' compensation system, insurance programs could be administered by states themselves or by private insurers, and states would be free to fashion different solutions in line with their own insurance and medical practice regulations. Coordination could be achieved by allowing state variation within an overall framework of national guidelines and objectives. Because of its privatization potential, the system would not necessarily require formation of immense new governmental agencies to enforce clinical safety and administer payments into and out of the system.

A system based on the above design principles offers promise in addressing the two key barriers to selective risk management.

⁸⁸ Brennan & Rosenthal, *supra* note 37, at 216-18.

a. Promoting Clinical Compliance Through an Insurance Framework

An insurance framework, properly designed, can promote clinical compliance while preserving needed flexibility. Physicians still would have discretion to disregard information contained in drug labeling, in situations where a physician deems this to be in the patient's best interest. By analogy, car insurance policies do not limit a driver's discretion to exceed the speed limit, nor do speeders necessarily suffer rate increases, so long as the drivers speed with sound judgment and manage to avoid accidents and police citations. In the same way, an insurance-based framework does not impose stark rules that interfere with the practice of medicine, nor would physicians automatically face rate increases for disregarding safety warnings, so long as their actual outcomes data show sound clinical judgment was applied in the decisionmaking process.

Safety provisions of drug labeling are enforced implicitly, but not rigidly, under an insurance-based framework. Consistent disregard of safety warnings would tend to result in higher premiums or loss of coverage, yet manufacturers and physicians still would have the flexibility to devise individual strategies for managing drug-related risks and could tailor these strategies to their specific products and patients.

b. Creating Investment Incentives and Spreading the Costs of Improved Safety

An insurance framework allows desired behaviors to be rewarded through reductions in premiums, thus creating timely, direct incentives to invest in safety improvements. For example, manufacturers could be encouraged to provide safety education for physicians, and physicians could be encouraged to attend such programs, by offering lower insurance premiums upon completion of the training. More generally, when premiums are experience-rated, manufacturers and physicians have a direct incentive to improve clinical safety. This is in contrast to incentives created under the tort system, which provides only a weak correlation between actions and consequences.⁸⁹ Investing in safety improvements may or may not translate into reduced tort claims. An insurance framework, on the other hand, can be structured to provide a dependable expectation that reducing the rate of injuries will translate into lower premiums.

Insurance frameworks have the attractive feature of being able to spread the costs of drug safety and mobilize funds for investment in safety projects. Even if the insurance framework initially limits its focus to manufacturers and physicians, there are sound reasons to aim for more inclusive coverage eventually. As additional covered parties (e.g., hospitals, pharmacists, and clinical laboratories) are brought into the insurance framework, additional premiums would be paid into the system and wider cost-spreading would be achieved. A portion of these premiums then could be set aside to invest in projects that offer general safety benefits, such as work to promote interoperability of clinical information systems, basic research into genetic and other causes of adverse drug reactions, and clinical safety efforts by AHRQ and CERTs. This financing mechanism could help overcome the free-rider problem and achieve fair cost sharing in projects that provide common benefits.

IV. CONCLUSION

There are serious, fundamental problems with the current legal framework for drug safety in the United States, and minor edits will not fix these problems. Designing a

⁸⁹ Localio et al., *supra* note 50.

drug-injury compensation framework would be a major undertaking and would require careful study and deliberation over a period of years. It is premature to propose that an insurance-based framework be implemented now; however, the idea is ripe for intense and systematic study.

Safe use of drugs in clinical practice requires nuanced, proactive management of risk and an ongoing, dynamic regulatory process that extends past the initial marketing approval as a matter of course, rather than in response to drug safety scandals. The current U.S. framework for drug safety regulation is binary, reactive, and incomplete, because it lacks the tools to keep beneficial drugs available while selectively managing their risks. The necessary tools include an improved framework for clinical compliance, an adaptive standard-setting process for clinical drug safety, and mechanisms to promote investment in safety-related projects. An insurance-based framework offers promise as a way to address longstanding problems in these areas.

Properly designed, an insurance-based framework could promote active management of drug safety risks to which patients are exposed, while preserving the benefits that prescription drugs offer to many patients. An insurance-based framework could help free the U.S. system from historical constraints that thwart effective risk management and would anticipate the science of increasing individualization of therapy in the twenty-first century.

